Clinical review

Fortnightly review

Drug treatment of epilepsy

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It is conventional to speak of someone having epilepsy, but it might be better—particularly in relation to promoting better drug treatment—if we were to think in terms of one of the epilepsies. Appropriate management requires not only that doctors differentiate between epilepsy and other similar attacks but also that they identify correctly patients' seizure types and, in some cases, the syndrome (for example, juvenile myoclonic epilepsy). A detailed discussion of the differential diagnosis is outside the scope of this review. However, it is worth emphasising that the diagnosis is usually made from the description of the episodes obtained from the patient or eyewitnesses, or both. This information is often, but not always, supported or supplemented by findings from electroencephalography. Information on diagnosis, investigations, and general principles of treatment can be found in textbooks,[1 2] and videos illustrating different types of seizure are now fairly readily available. Ideally, the diagnosis should be made or confirmed by a specialist, who will also advise on treatment. Nonetheless, doctors who do not have a specialist interest in epilepsy will often be required to take a hand in treatment. This brief review is intended primarily for them.

Summary points

- In treating epilepsy, the drug chosen needs to be matched to the individual patient and the type of epilepsy
- Often, the most suitable treatment regimen can be established only by trial and error
- The wide range of treatments now available offers most patients good seizure control without unacceptable side effects and offers patients with refractory epilepsy a chance of better control
- Many patients with epilepsy still do not seem to be getting the treatments that are most appropriate for them

Methods

As a clinical pharmacologist with some training in neurology, I have been running an epilepsy clinic for many years. This review is based on a synthesis of my personal experience, information from published studies, and opinions imparted by other epilepsy specialists in publications and at recent conferences. I have selected references to support important points and to provide access to additional information, including opinion that differs (in shade at least) from my own.

ANGELA SMITH

Choosing a drug

Even in this era of evidence based medicine, there is an art as well as a science in choosing the best drug treatment for patients with epilepsy. The choice of treatment needs to be matched to the patient—for example, whether they are pregnant or potentially childbearing, elderly, or overweight—and to the type(s) of seizure they have (table 1). Often, the most suitable treatment for an individual can be established only by a process of trial and error. Table 2 gives an overview of the current drugs used in treating epilepsy.

Established drugs

Carbamazepine

Carbamazepine is used for patients with partial seizures, generalised tonic-clonic seizures, or both.[3] Provided carbamazepine is introduced gradually, tolerability is relatively good in children and younger adults. If further seizures occur, the dose is titrated upwards until the seizures are controlled or the patient starts to have side effects of unsteadiness or drowsiness that necessitate limiting the dose. The maximum tolerated dose should be determined by the patient's symptoms rather than by monitoring the

Table 1 Choices for early treatment of the more common types of epilepsy

Seizure type	Drug(s) of choice	Alternative drug(s)	Reasons for using (examples)
Partial seizures	Carbamazepine* or valproate	Valproate	Elderly patients Women taking contraceptive pill Carbamazepine "failures"
	Lamotrigine?†	Carbamazepine	Obese patients Valproate failures
		Lamotrigine	Carbamazepine or valproate not suitable Childbearing women
Generalised tonic-clonic (grand mal) seizures:			
Secondary to partial seizures	As for partial seizures	As above	As above
With absences or/and myoclonic seizures	Valproate	Lamotrigine	Valproate not suitable Childbearing women
Without evidence of other seizure type(s) or focal onset‡	Valproate§ or carbamazepine	The other or lamotrigine	As for patients with partial seizures (above)
	Lamotrigine?†		As for patients with partial seizures (above)
Absence (petit mal) seizures	Valproate	Ethosuxemide or lamotrigine	

*Some studies[18] (but not all[19]) suggest that carbamazepine is somewhat more effective than valproate for partial seizures.
†Specialists, familiar with the drug, now (sometimes) use lamotrigine as a first choice.
‡Electroencephalogram may be normal or show an abnormality that suggests "primary generalised" epilepsy.
§Most specialists would choose valproate for grand-mal seizures due to "primary generalised" epilepsy.

drug concentration. Somewhat before the maximum tolerated dose is reached, patients may complain of transient double vision or blurred vision; they may be prepared to put up with this provided the drug is effective. These adverse effects can often be alleviated by changing to the modified release formulation of the drug—although there is then an increased risk of seizures.

Many patients are allergic to carbamazepine and develop a rash, but systemic symptoms are not usually severe. Carbamazepine causes enzyme induction, which may result in drug interactions (for example, with the contraceptive pill). Carbamazepine may also be the "victim" in drug interactions that arise through enzyme inhibition (for example, with erythromycin). The drug has teratogenic effects; it is implicated in spina bifida.

Valproate

Valproate is effective in generalised tonic-clonic seizures and partial seizures and can be used to treat a wider range of seizure types than carbamazepine.[3] Valproate is a drug of choice for absences and myoclonic seizures. Although there is no need to build up gradually to a therapeutic dose, the dosage may need to be titrated upwards according to the patient's response. The upper end of the recommended dosage range is 3 g/day, but patients are likely to complain of unacceptable side effects such as sedation, weight gain, or tremor well before this dose is reached. One advantage of valproate is that it does not cause enzyme induction. It is an enzyme inhibitor, an important fact when lamotrigine is used concurrently. Unfortunately, valproate is also teratogenic and is implicated in spina bifida. Valproate is a drug of choice for seizures in elderly people.[4] A modified release formulation (Epilim Chrono) offers the convenience of a single daily dose, but claims that this improves compliance compared with a twice daily regimen may be exaggerated.

Table 2 Overview of current drug treatments for epilepsy

		Knowledge required by non-specialist doctors		
Drug	**Resumé**	**Know of**	**Know about**	**Know how to use**
Carbamazepine	Premier league: for partial or generalised tonic-clonic seizures. Tolerability generally good in children and younger adults, relatively less good in elderly people. Allergic reactions (rash) fairly common. Enzyme inducing drug	Yes	Yes	Yes
Valproate	Premier league: for generalised (both tonic-clonic and absence) and partial seizures. Weight gain often a problem. Allergic reactions uncommon. Not an enzyme inducing drug	Yes	Yes	Yes
Lamotrigine	Recently promoted (monotherapy licence), wide spectrum of activity; may join first league. Allergic reactions (rash) fairly common and occasionally severe	Yes	Yes	Perhaps
Phenytoin	Formerly in premier league, now used less because of side effects. Spectrum of activity similar to carbamazepine. Narrow therapeutic window plus complex pharmacokinetics demand monitoring of drug concentration	Yes	Yes	Perhaps
Vigabatrin	Recent warning about visual field defects makes specialist review desirable (patients may require visual field testing)	Yes	Perhaps	–
Gabapentin	Not very effective as additional treatment in severe epilepsy, but may have a future as monotherapy	Yes	Perhaps	–
Clobazam	Has valuable special uses, particularly when seizures occur in clusters	Yes	Perhaps	–
Topiramate	For treating severe epilepsy	Yes	–	–
Tiagabine	Just launched in Britain; place in clinical practice still to be established	Yes	–	–
Phenobarbitone	Formerly used widely in cases of refractory epilepsy; may still have a role when other treatments fail. Specialist opinion on withdrawal of drug is advisable	Yes	Perhaps	–
Primidone	Formerly used widely in cases of refractory epilepsy	Yes	–	–
Clonazepam	Formerly used widely in cases of refractory epilepsy; may still have a role when other treatments fail. Specialist opinion on withdrawal of drug is advisable	Yes	Perhaps	–
Ethosuximide	Alternative to valproate for petit mal seizures only	Yes	Perhaps	–

Information on doses for adults and children can be found in the *British National Formulary* and in Brodie and Dichter,[3] Dichter and Brodie,[6] and Stephen and Brodie.[7]

Phenytoin

Phenytoin has fallen from favour because side effects are more of a problem than with carbamazepine or valproate.[3] It has not been shown to be less effective than those drugs or the new drugs which most British epilepsy specialists would now be inclined to try first. At the risk of oversimplification, there are two basic problems with phenytoin. Side effects such as hirsutism, gum hypertrophy, and aggravation of acne occur during chronic use even in patients whose phenytoin concentration is in the therapeutic range. The second problem is phenytoin intoxication: because dose adjustments produce disproportionately large changes in blood concentrations and its metabolism varies considerably between individuals, many patients show symptoms and signs of intoxication at some point. This is most likely to occur after injudicious dose adjustment.

For optimal phenytoin treatment, the patient's blood phenytoin concentrations must be monitored at some point. Indeed, a standard starting dose (for example 300 mg/day in an adult) has the potential to produce a concentration that is either too high or too low in over half of the population. It is therefore advisable to check the blood phenytoin concentration about two weeks after starting treatment.

Although few British specialists recommend phenytoin nowadays, it is still widely used, and many doctors are likely to encounter patients taking it.[5] Doctors still need to know enough about phenytoin to be able to adjust the dose correctly. We should not abandon phenytoin. It may still have a place in severe epilepsy when other, "kinder," treatments have failed, and its effects on physical appearance are less evident in elderly people, among whom it seems to be as well tolerated as valproate.[4] Phenytoin too is teratogenic; its effects include cardiac defects and cleft lip or palate.

New drugs

Four new drugs for epilepsy (vigabatrin (Sabril),[6–8] lamotrigine (Lamictal),[6 7 9] gabapentin (Neurontin),[6 7 10 11] and topiramate (Topamax)[6 7 12]) have been licensed in the United Kingdom within the past 10 years. (Another new drug, tiagabine (Gabitril), has just come on the market.[6]) All four drugs were licensed as "add on" treatments and are still used as such, but lamotrigine is now licensed as a monotherapy too. Though there are some differences between these drugs with regard to less common types of epilepsy,[6 7] they are all competing for a market share in the treatment of patients with partial seizures, with or without secondarily generalised tonic-clonic seizures, who have not responded to drugs such as carbamazepine and valproate.

None of these newer drugs is best in all or most cases; any one of them may work in cases where others have not, and in many cases of severe epilepsy none will prove satisfactory. There have not been any head to head trials comparing these drugs, and there is no scientific basis for stating that one is more effective than another.[13] That is not to say that experienced epilepsy specialists regard them as pretty much the same. Brodie has produced a "star rating system" covering the new drugs and also the older treatments.[14] Additional information, including many practical points on using these new drugs, can be found in a recent article.[7]

Lamotrigine

Lamotrigine has been on the market for about seven years.[6 7 9] As time has passed, specialists have been prescribing it more often and earlier, sometimes as the first treatment. One of the main advantages of lamotrigine is that it causes little cognitive impairment or overt sedation compared with other treatments.[6 9] It sometimes has an arousing or alerting effect. In some patients, mainly elderly people, this may manifest itself as unwanted agitation. Lamotrigine has a wide spectrum of activity. The chief drawback is the risk of allergic reactions. These occur less often than is the case with carbamazepine, but they are more often severe and can be life threatening, although this is rare.

Introducing lamotrigine gradually is one of the keys to reducing the frequency and severity of allergic reactions. Patients already taking valproate, which inhibits lamotrigine metabolism, are prescribed a lower dose than patients taking carbamazepine or phenytoin and those given lamotrigine as monotherapy. There often seems to be synergy between lamotrigine and valproate, over and above that expected from the pharmacokinetic interaction. I find lamotrigine very useful in some elderly patients, and quite low doses may be optimum in this age group. At the time of writing, lamotrigine seems to carry a low risk of teratogenic effects.

Vigabatrin

Vigabatrin was licensed before lamotrigine.[6–8] Because it was the first new add on drug, it has been tried with many patients with longstanding epilepsy. As well as proving effective in some of these patients, it is particularly useful in some childhood epilepsies and has become a drug of choice for infantile spasms.

Recent reports that vigabatrin causes visual field defects are a major setback.[15] On the basis of the information currently available, it would not be appropriate for doctors to rush to withdraw this drug from patients who have benefited greatly. However, patients need to be reviewed by their specialist for an assessment of risk and benefit, and some form of visual field testing will be required for those who continue to take vigabatrin. This presents a problem in children and those with learning difficulties. At the moment, especially where alternative treatments are available, it seems wise to be cautious about giving vigabatrin to additional patients.

Gabapentin

Gabapentin was promoted initially with a standard dosage regimen of 300 mg or 400 mg three times daily.[6 7] It has become clear, however, that many patients benefit only when doses two or more times those mentioned are reached, usually after a gradual build up.[10 11] Nonetheless, the overall impression of the balance of efficacy and toxicity, compared with the other three newer drugs, remains largely unchanged: gabapentin seems less effective, but also less toxic. Consolation for its manufacturers may lie in the fact that patients with epilepsy of recent onset require a drug without many unpleasant side effects and may not need a very potent one. Gabapentin may come into its own when it is used earlier and as monotherapy.

Topiramate

Topiramate has now been on the market for a few years, and its effects seem to be at the other end of the spectrum from those of gabapentin—that is, it is potent and more toxic.[6 7 12] This is another drug where gradual introduction over some months helps to reduce side effects. Nevertheless, many patients are unable to tolerate an effective dose of topiramate. The main problems are psychological or cognitive changes, sometimes accompanied by difficulty in finding words, which may be devastating for patients' self confidence. In addition, topiramate has to be stopped in some patients who are otherwise tolerating it well, because of weight loss. For the foreseeable future, topiramate remains a treatment to be prescribed by the experienced specialist.

Other drugs

Barbiturates

Nowadays, phenobarbitone (or primidone) is unlikely to be used early in treatment and may be considered a drug of last resort.[3] Phenobarbitone is cheap, easy to use, and effective, but it is notorious for causing cognitive impairment, often with sedation in adults, and it makes young children hyperactive. Many patients with epilepsy are still taking a barbiturate.[4] Some of them no longer need treatment and others would be better taking a different drug. Patients taking a barbiturate should be reviewed by a specialist. For many, particularly those whose epilepsy is not controlled or who have side effects, this should lead to a change in treatment. For others, especially older patients without any overt problems, the best advice may be, "If it works, don't fix it."

Clonazepam

Clonazepam was fairly widely used in the 1970s to treat epilepsy that was difficult to control, and it may still have a place as an alternative treatment in some of the myoclonic epilepsies of childhood.[3] It is quite sedative and has therefore to be introduced gradually. As with other benzodiazepines there are also problems of tolerance and dependence. Clonazepam should be withdrawn gradually to avoid precipitating seizures.

Clobazam

Clobazam is much less sedative than clonazepam and is used by epilepsy specialists as a "trick of the trade."[3] It is often effective in the short term and can occasionally be effective long term as adjunctive therapy. Clobazam's usefulness is usually limited by the development of at least partial tolerance. Because tolerance takes a little time to develop, however, clobazam can be very useful in short courses; as an adjunctive treatment in patients whose seizures occur in clusters; to prevent exacerbations around menstruation in catamenial epilepsy[16]; and to ensure control for important occasions such as holidays in patients with refractory epilepsy.

Errors still occur

The wide range of treatments now available offers many patients seizure control without unacceptable side effects and provides the minority who have refractory epilepsy with more chance of achieving better control. However, personal experience, a recent review of prescribing patterns,[5] and the testimony of patients[17] seem to indicate that many people with epilepsy are not getting the treatments most appropriate for them. Common and potentially avoidable errors in treatment are given in the box.

Common treatment errors

- Incorrect or incomplete identification of seizure type(s), resulting in inappropriate choice of treatment—for example, confusion between brief complex partial seizures and absences or failure to recognise juvenile myoclonic epilepsy
- A drug appropriate for the patient's seizure type(s) is chosen, but it is not appropriate for that patient—for example, phenytoin for an adolescent or valproate for a woman likely to become pregnant
- The diagnosis and choice of drug are correct, but the patient is given too low a dose (for example, only the "starting" dose is tried) or the patient is given too high a dose too quickly (for example when starting carbamazepine)
- The epilepsy is controlled, but the patient has problems with side effects and no change in the treatment (drug or dosage) is made
- The patient is seen by a specialist and referred back to the general practitioner with an appropriate recommendation regarding treatment, but when this proves ineffective further advice is not sought

Competing interests: During the past five years MF has attended epilepsy meetings abroad as a guest of the manufacturers of all four of the "new" drugs currently marketed in the United Kingdom.

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